Severe exacerbations and acute respiratory failure in COPD

Impact paragraph

Impact paragraph

The present chapter describes the scientific and social impact of this thesis. Otherwise, a description of the impact of the created value from the gathered knowledge by making it suitable for and/or available in clinical practice and translating that information into practical services, products or tools. First, the aims and main findings of the thesis are briefly described. Next, the scientific and public relevance and its impact on clinical practice are discussed. Thereafter, target groups of this thesis are mentioned. Finally, activities and opportunities will be discussed.

Aims and main findings of this thesis

Severe exacerbations of chronic obstructive pulmonary disease (COPD) have a detrimental impact on patients with this disease and impose a great burden on healthcare systems and societies. In order to improve management and outcomes of these events, this thesis aimed to investigate short- and longer-term mortality rates for COPD patients hospitalized for exacerbations with or without acute respiratory failure. The second aim of the thesis was to identify predictors for poor outcomes and to analyze the effects of non-invasive ventilation (NIV) in the acute and post-acute phase of severe exacerbations. Finally, the thesis investigated gastro-intestinal permeability in relation to exacerbations, as alterations in gut barrier function might be causally related to these events.

In four chapters of this thesis, high mortality rates following hospitalization for COPD exacerbation were shown in different patient populations. These vary from approximately 6-14% for inpatient mortality, to 16-30% after three months, 28-44% after one year and >70% after more than ten years of follow up. The thesis shows that the hospitalized COPD population is heterogeneous regarding disease severity and need for medical management, which probably accounts for the variation in mortality rates between different chapters.

Several independent predictors for mortality following hospitalized COPD exacerbations were identified in this thesis, including age, male gender, poor lung function, increased arterial carbon dioxide levels, previous exacerbations, co-occurring diseases and low body weight. A risk stratification tool for 90-day mortality was developed in this thesis and included four of these factors.

The effectiveness of long-term nocturnal NIV in patients with COPD with prolonged hypercapnia after ventilatory support for acute respiratory failure was investigated in this thesis and was negative regarding its primary endpoints: time to readmission for respiratory causes or death.

Increased small intestine permeability was observed COPD patients hospitalized with acute hypoxemic respiratory failure, while in another chapter, reduced gut integrity was observed in stable COPD patients in comparison to controls, with no association with the occurrence of exacerbations.

Relevance

The results regarding the impact of severe exacerbations on in-hospital, short- and long-term mortality and their predictors are highly relevant for the scientific community. They raise awareness among scientists and enforce the need for research in this field of COPD to study interventions to modify the risk factors for poor outcomes and reduce mortality. Possible traits that were identified in this thesis and that could be accessible for intervention include (accelerated) aging, low body weight, increased arterial carbon dioxide, comorbid conditions and poor lung function.

The negative results regarding the early initiation of NIV following ventilatory support, contributed to the better understanding of the target population for NIV and the development of subsequent intervention studies by other scientific groups in this field. Ultimately, this has resulted in the implementation of NIV in the management of severe COPD with chronic respiratory failure.

The observations regarding alterations in gut function in COPD patients and the association with exacerbations help to increase scientific awareness regarding the systemic consequences of COPD and the need for a holistic approach if scientists aim to unravel the complex pathophysiology of COPD and discover targets for innovative, potentially disease-modifying, interventions.

Target groups

In addition to the scientific community, the main target group of this thesis are the clinicians such as the pulmonologists, intensive care physicians and general

practitioners, who are involved in the management of the COPD patients. Other health care providers who are involved in caring for COPD patients like physician assistants, nurse practitioners and respiratory nurses are also a target audience. For these health care workers, the results of this thesis point out the impact of severe exacerbations and the need to optimize patient management in order to reduce this impact. Also, the results of this thesis provide them with knowledge regarding treatable patient characteristics if they aim to reduce mortality risk. With the risk stratification tool provided in this thesis, clinicians have the opportunity to assess the adverse outcome on admission and this tool may support shared decision making and advance care planning leading to personalized medicine. Also, the results of this thesis highlight that patients with at first sight mild or moderate COPD may develop acute respiratory failure and need for NIV.

Pharmaceutical companies might be interested in the potentially modifiable traits associated with mortality in severe exacerbations in their search for targets for novel medications. This also applies to organizations involved in the development of non-pharmacological interventions.

From an educational point of view the results of the thesis are also relevant. For students and trainees, they provide important information about the tremendous impact of COPD on mortality and its determinants, the positioning of NIV and some of the systemic aspects of the disease.

Moreover, the results of this thesis are relevant to patients and their informal caregivers. They emphasize the importance of preventing severe exacerbations and give them insight in the predictors of poor outcomes. Also, they demonstrate to patients that COPD is more than a respiratory disease, demanding a more holistic approach.

Furthermore, the reported detrimental impact of severe exacerbations in this thesis is relevant for health care policy makers and payers and could result in prioritization of COPD management and reinforcement of health care resources and development of innovative programmes to change this trend.

Activities

The demonstrated results of the thesis have led to several activities in this domain of research and field of expertise. The findings of **chapters 3** to **9** were transformed into original manuscripts and published or submitted in different scientific international journals. Moreover, several experts in the field wrote editorial letters to highlight on these manuscripts, especially to the manuscripts of **chapter 4**, **5** and **7**. Furthermore, the results presented in **chapters 3** to **9** were presented during the annual European Respiratory Society (ERS) congresses in 2013 (Barcelona, Spain), 2014 (Munich, Germany), 2016 (London, United Kingdom), 2017 (Milan, Italy) and 2020 (virtual, Vienna, Austria). The knowledge presented in this thesis is also used in daily clinical practice at the department of Respiratory Medicine in Maastricht UMC+ and included in the education of trainees during the round table visits and of medical and other students at Faculty of Health, Medicine and Life Sciences of Maastricht University. As a consequence of these activities, the findings of the thesis have been distributed broadly and hopefully this thesis will support clinicians identifying new clinically-related questions, inspire researchers for innovative studies and raise awareness among policy makers and payers regarding the personal and societal burden and subsequent needs associated with severe COPD exacerbations.